

Naturally, the solution is cooled after heating before separating the crystallized products and solids but the temperature at which crystallization occurs may be above 60°C. Examples conducted at elevated temperatures are given in Examples 7-11.

Background

The present invention is directed to crystalline salts of 5-methyltetrahydrofolic acids (claims 1-7) and methods for their production, (claims 8-13 and 16-20). The crystalline forms of these salts have been found to exhibit excellent stability, (see page 2, lines 5 and 17-18 of the specification). Crystalline specimens were compared with amorphous specimens in Example 1 and are shown to provide higher stability. Figures 1-5 of the application show the differences in the diffraction spectra (X-Ray Powder Plots) of crystalline samples and amorphous samples of 5-methyltetrahydrofolic acid. As stated on page 3 of the specification, crystallization is preferably effected from solutions of this salt of 5-methyltetrahydrofolic acids but can also be effected from a suspension. Crystallization of the salts occurs spontaneously or by seeding. Different crystalline forms are obtained by thermal treatments as discussed more particularly on page 3, lines 24-32.

Rejections Under 35 USC §102(b)

Scheib (U.S. 5,457,202)

The compounds claimed in claims 1-3 of the present application differ in various points from those disclosed by Scheib (U.S. 5,457,202). One difference is that the present application claims crystalline salts of 5-methyl-(6R,S)-, -(6S)- and -(6R)-tetrahydrofolic acid. Scheib does not describe a crystalline salt of 5-methyltetrahydrofolic acid nor gives any attribute of the described salts which suggests they are crystalline. Within US 5,457,202, column 1, lines 44-52, a process of the isolation/separation of the solid product from the liquid solution is repeatedly described as "precipitation." For example, at column 1, lines 47-48, it is stated that, "This results in precipitation of the salt of the acid with the pyrrolidine derivative." At column 1, lines 51-52, it is stated that "the salt of the 6S-acid precipitates again on cooling the solution." There is no indication the salt solution is seeded with the crystalline form or that crystals are grown from spontaneously formed crystals of the salts of 5-methyltetrahydrofolic acid.

The process parameters within US 5,457,202 are also characteristic of precipitation and not crystallization. For example, in Example 1, column 1, lines 66-67, it is described that "the reaction mixture ... is stirred vigorously." This stirring is not consistent with growing crystals in solution.

These processes can also produce products which show totally different behaviors. The crystallization methods employed in the present invention permit the formation of racemic 5-methyl-(6R,S)-tetrahydrofolic acid salts, see for example, Example 5 of the specification. In contrast, the product produced according to the methods of Scheib (US 5,457,202) always results in the separation of optical isomers, which are clearly distinct from the crystalline form of the compounds defined in claims 1-3.

It is also alleged that the methods of claims 8 and 10-14 are anticipated by Scheib. These methods define a method of producing crystalline salts of 5-methyl-(6R,S), -(6S) - and 5-methyl(6R)-tetrahydrofolic acid by crystallizing these salts from a polar medium after thermal treatment. As discussed above, the process parameters of Scheib are characteristic of "precipitation" and not crystallization. It is alleged that Examples 2-4 of Scheib describe "recrystallizing" n-5-methyltetrahydrofolic at 85°C. It is noted that, "the sparingly soluble 6R-salt was filtered off with suction" ... "after cooling to 60°C." The mother liquor was cooled to 20°C and the resulting crystals filtered off with suction and washed with water. There is no indication the products obtained are crystalline or exhibit any degree of crystallinity and there is also no indication the product is "recrystallized" as alleged. The procedures described are consistent with the precipitation methods discussed above. Therefore, Scheib does not anticipate method claims 8 and 10-13.

Claim 10 is further distinguished from teachings of Scheib in that the thermal treatment required is at a temperature above 85°C. The examples described by Scheib (Examples 2-4) describe heating the salts to 85°C.

Müller US 5,006,655

It is alleged that the compounds disclosed in claims 1-3 are anticipated by Müller ('655) on the basis that Müller describes techniques of crystallizing and recrystallizing the calcium salt of 5-methyltetrahydrofolic acid. Specific reference is made to the dihydrate and pentihydrate forms disclosed on lines 42 and 50 of column 7, respectively. The terms

“crystallizing” and “recrystallizing” used by Müller '655 are misleading. These terms refer to the recovery of the solid within a liquid and separating the solid from the liquid. There is no indication that the product formed has a crystalline structure. The techniques employed suggest the structure is amorphous since the pH value of about 4 employed in the Example referred to at column 7 (Example 2) corresponds to a pH value where 5-methyltetrahydrofolic acid shows its lowest solubility. Therefore, the separated 5-methyltetrahydrofolic acid salt will be expected to be a precipitate and not a salt crystal. No mention is made of seeding the solution to initiate the formation of salt crystals. In the absence any reference to the crystalline properties of the products obtained by Müller, this reference does not anticipate the subject matter of claims 1-3. The product produced by Müller would more likely be amorphous. The dihydrate and pentahydrate formed referred to by Müller do not necessarily correlate to a crystalline form but can refer to the complex form of the salt. In that the disclosure of Müller et al. does not mention the crystallinity of the isolated salt obtained and the methods disclosed do not inherently provide such crystallinity, this reference does not anticipate the subject matter of claims 1-3 herein.

Marazza et al. US 5,194,611

Marazza '611 allegedly anticipates the compounds of claims 1 and 2 herein on the basis that Examples 1 and 2 of the reference describe the separation of a mixture of (6R,S)-diastereoisomers. These separation techniques are not shown to form particles which have crystallinity. The process parameters given in Example 1 of Marazza show the solution is evaporated to obtain the product in the form of a honey like or glass like solid. Evaporating the solution to reduce solubility by the removal of the solvent is not consistent with crystallization techniques. In addition, the procedures of Example 2 show the addition of absolute ethanol prior to separation tends to reduce the solubility of the solids within the solution. Reducing the solubility is consistent with a precipitation technique and not crystallization. In the absence of any disclosure of the crystalline form for the products obtained, Applicants submit Marazza '611 does not anticipate the compounds of claims 1 and 2.

Vecchi US 5,350,850

It is alleged that claims 1-3 are also anticipated by Vecchi '850. As with the U.S. patents discussed above, Vecchi '850 makes no reference to the crystallinity of the recovered 5-methyltetrahydrofolic acid. The terms "recrystallization" and "crystallization" refer to a method of separation of a solid from a liquid as is evident by the language at column 3, lines 47-49 wherein it is said "the solution is cooled to +10°C and the final product is lead to crystallize until it is completely precipitated." Here crystallization is equated with "precipitation" therefore, reference to recrystallization at column 4, lines 5-13 does not refer to the growth of crystals of the calcium salt of 5-methyltetrahydrofolate but rather the separation of the solid from the liquid. Therefore, the crystalline compounds defined in claims 1-3 herein are not anticipated by this reference.

Claims 8, 10, 11, 13, 16 and 17 are directed to methods and are said to be anticipated by Vecchi '850 as well. It is alleged the reference teaches the process of heating the calcium salt in the water above 85° and affecting recrystallization at column 4, line 5. As discussed above, Vecchi equate recrystallization with precipitation such that the product obtained is not necessarily crystalline. This is established at column 3, lines 50-51 where the product of the process is described as being very sensitive to light and oxygen. In contrast, the crystalline products according to the present application show extremely high stability values. Furthermore, the products of US 5,350,850 are said to be practically insoluble in water (see column 4, lines 9-10). The products of the present invention however show quite high solubility in water of between 1% (type 3) and 3.8% (type 2) at 20°C (see for example, Example 3). In addition, Vecchi does not distinguish between the products obtained from processes carried out at temperatures below room temperature and the products obtained by processes at elevated temperatures. Applicants have shown that the temperature employed can affect the crystalline form of the product obtained. Since no distinction is made by Vecchi, it can be assumed that the products are amorphous. Therefore, there is no indication that the methods of Vecchi form crystalline products of the 5-methyltetrahydrofolic acid and therefore they do not anticipate the subject matter of claims 8-13 and 16-20.

Gennari US 5,223,500

It is alleged that claims 1 and 3 are anticipated by Gennari '500. It is alleged that Example 7 of this reference in lines 1-28 at column 7 teach a compound of a calcium salt of 5-methyltetrahydrofolate with more than 3 or more molecules of crystallization and racemic 5-methyltetrahydrofolate. Again the reference provides no reference to the crystallinity of the 5-methyltetrahydrofolic acid produced. Although the salt referred to in column 7, line 24 it said to be “crystalline”, it is also said to be “precipitated” and not grown as is characteristic of crystals. The amorphous characters for products produced by Gennari is evident by the disclosure at column 4, lines 31-38 wherein it is stated that the production process for the 5-methyltetrahydrofolic acid should be conducted in the presence of an inert gas to prevent self oxidation. The stabilized compositions referred to at column 4, lines 50-52 also require a stabilizer as described at column 4, lines 53-60 which is inconsistent with the crystalline products claimed herein.

Claim 5

Claim 5 is separately rejected under 35 USC §102(b) based on Müller '655 referred to above. This reference is said to teach the “dihydrate” at column 7, line 42. There is no indication the dihydrate has a crystalline form.

Claims 6 and 7

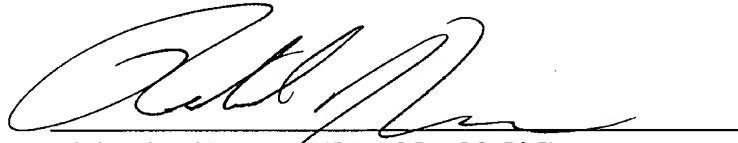
Similarly, Müller ('655), Vecchi ('850) and Gennari ('500) and Scheib ('202) allegedly anticipate claims 6 and 7 drawn to 5-methyltetrahydrofolic acids as type-3 and type-4 pentahydrates. Müller ('655) allegedly shows a pentahydrate at column 7, line 50, Gennari ('500) allegedly shows a pentahydrate at lines 26-17 of column 7. It is not clear where Scheib ('202) describes pentahydrates and it is not seen where Vecchi ('850) describes pentahydrates. However, as discussed above none of these references described a crystalline properties of the products obtained. While some of the references describe pentahydrate forms, these are not shown to be crystalline in structure. Therefore, the 5-methyl-(6S)-tetrahydrofolic acids described by these references do not inherently have the two theta values recited in claims 6 and 7 and so do not anticipate these claims.

Applicants acknowledge the allowability of claims 4 and 18-20 if written in

independent form. The above amendments accomplish this purpose.

Based on the above remarks, Applicants submit that claims 1-13 and 16-20 are in a form suitable for allowance and patentable over the cited references. Therefore, withdrawal of the rejections and allowance of these claims are earnestly solicited.

Respectfully submitted,



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